PREGNANCY

The use of alcohol and illicit drugs during pregnancy has been associated with increased mortality and morbidity for the mother, foetus and subsequent infant. Viewed critically, however, it becomes apparent that this increase in morbidity and mortality is due to a complex interaction of multiple factors and not always due directly to the effect of the substance. Though pregnancy may act as a catalyst for change, drug misusers may not use general health services until late into pregnancy and this increases the health risks for both mother and child. Women in general, and pregnant women in particular are under-represented in drug services, and this is related both to a fear of interference related to child protection, and to practical difficulties related to mothering responsibilities. The first rule of management is to engage the mother with services: through close coordination between the various different care agencies, the quality and quantity of antenatal care delivered can be increased, which has been demonstrated to have long-term positive effects for both mother and child. Following birth, infants should receive specialist paediatric care to assess and manage the various complications that may occur in the neonatal phase; the mother (parents) should be involved in this assessment and on-going management and treated in a supportive and non-judgmental manner. It is generally recognised as good practice for local obstetric departments to have formal links with local drug specialists, GPs and social services in the form of a written policy.

- Substance misuse during pregnancy is associated with but not necessarily causal for increased mortality and morbidity in the mother and child.
- The amount of antenatal care provided is directly correlated with outcome for the neonate; thus the key aim of management is to attract the mother into health care treatment services and to provide antenatal care.
- The medical treatment of choice for the mother is detoxification, apart from in opiate dependency, where methadone maintenance has been the treatment of choice for the last 30 years. Obstetric ward in-patient opiate detoxification may be appropriate in some cases.
- Subutex should not be initiated in pregnancy. Where a woman becomes pregnant whilst already prescribed Subutex, a judgement will have to be made regarding its continuation, taking into account the benefits and risks to the mother and foetus.
- The management of newborns of drug-dependent mothers should always occur in a specialist paediatric unit.
- Heavy benzodiazepine use, cocaine use, HIV and hepatitis C positive status are all **contraindications** to breast-feeding.
- Mothers who are prescribed methadone or who are carriers of hepatitis B should be **encouraged** to breastfeed.

OBJECTIVES OF CARE

The key aims of management are to attract the woman into health care treatment services, provide antenatal care and stabilise the substance misuse problem, either through detoxification or maintenance prescribing depending of the drug of use and the presentation. The amount of antenatal care provided is directly correlated with outcome for the neonate. There will usually be a planning meeting around the 32nd week of pregnancy, and if there are child protection concerns the relevant procedures may be set in motion following this.

EFFECTS OF DRUGS ON THE FOETUS

Potential risks to offspring exposed to alcohol and other drugs in utero include morphologic teratogenicity (physical abnormalities), behavioural teratogenicity (enduring behavioural changes resulting from alterations in the developing central nervous system), foetal or neonatal withdrawal, foetal or neonatal toxicity and miscarriage or stillbirth. Intra-uterine growth retardation and pre-term deliveries contribute to increased rates of low birth weight and increased perinatal mortality rate. Cocaine use appears to be particularly associated with high rates of early pregnancy loss and third trimester placental abruptions (Chasnoff IJ et al, 1985) and heroin use appears to have a direct effect on foetal growth (Kaltenbach K, Finnegan L, 1997). However, in research, as well as in clinical practice, it is generally impossible to separate the direct adverse effects of these substances from associated changes in lifestyle, nutrition, medical illness and social support.

METHODS USED TO DETECT SUBSTANCES IN THE NEONATE

The usual laboratory techniques and body matrices can be used (see Section E7). In addition, the use of meconium (neonate's first stool) offers a noninvasive means of testing the neonate.

SUBSTANCE SPECIFIC MANAGEMENT DURING PREGNANCY

ALCOHOL

No safe level of alcohol consumption in pregnancy has been established, although it is generally believed that consumption of more than 12 units of alcohol daily, especially in a binge drinking pattern, holds significant risks for the foetus. In the USA, it has been estimated that foetal effects of alcohol are recognisable in 1 in 100 births, while the more severe foetal alcohol syndrome occurs in between 1 in 300 and 1 in 1000 births. The latter is characterised by high rates of mental retardation, neurological deficits and behavioural problems in the child.

The biological treatment of choice for the physically dependent pregnant mother is detoxification. This should generally take place in an in-patient setting with collaboration from an obstetrician. Patients who are physically dependent on alcohol should always be advised to avoid sudden cessation of alcohol consumption, and in the pregnant woman, there is the additional threat to the life of the foetus. Differentiation of symptoms of alcohol withdrawal from symptoms of pregnancy may be difficult, but tremor and fever should usually be specific for alcohol withdrawal.

For anything other than a mild physical withdrawal from alcohol, the use of medication to control withdrawal should be considered; uncontrolled withdrawal seizures, hypertension, tachycardia and agitation pose serious risks to both the mother and foetus and will nearly always require pharmacologic intervention.

Usually, the first choice agent will be chlordiazepoxide, or possibly diazepam. However, if high doses are required (>30mg diazepam equivalent in 24 hours), there is a risk of foetal or neonatal toxicity. External cardiac monitoring of the foetal heart will be required in such cases, under specialist obstetric care. If detoxification is taking place near the end of pregnancy, toxicity may present as 'floppy baby syndrome' which may be reversed with flumazenil under specialist obstetric/paediatric care. Conversely, if benzodiazepines are needed for more than a few days near the end of pregnancy, the newborn may show signs of benzodiazepine withdrawal, characterised by increased tone, hyperreflexia and tremor. This will usually resolve spontaneously without specific intervention.

There is no clear evidence to demonstrate any teratogenic effect of benzodiazepine use in pregnancy, and the bulk of the evidence suggests that the benefits of the short-term use of benzodiazepines for alcohol detoxification outweigh the risks posed by an uncontrolled withdrawal.

SEDATIVE-HYPNOTICS

As for alcohol, the treatment of choice is controlled withdrawal in an in-patient setting. As well as the usual, potentially life-threatening effects of an uncontrolled withdrawal to the mother, there is the additional risk of foetal respiratory arrest. Conversion to a long-acting benzodiazepine such as chlordiazepoxide, followed by dose-tapering, with specialist obstetric collaboration will usually be the treatment of first choice.

STIMULANT DRUGS

The treatment of choice is withdrawal due to the risks associated with cocaine misuse during pregnancy. There is no clear recommendation regarding the use of medication to assist withdrawal. In cases of extreme agitation, it may be prudent to prescribe low dose chlordiazepoxide, but such a decision must be made on a case-by-case basis.

OPIATES

In contrast to the other drug classes, the treatment of choice for opiate dependency in pregnancy is **methadone maintenance**. Such an approach is aimed at the primary goal of stabilising behaviour and enhancing engagement with antenatal care. In addition, opiate withdrawal may theoretically be associated with an increased risk of spontaneous abortion and premature labour. The overall evidence indicates that low dose maintenance is the best option for ensuring continuity of management of pregnancy and aftercare. However, higher doses may be required if non-prescribed opiate use persists or recurs. In the third trimester, many women will need an increased methadone dose because of various physiological changes and weight gain. Dividing the daily dose can sometimes overcome the need for an increase in the dose in the later stages of pregnancy. There is no clear relation between the intensity of neonatal withdrawal and maternal methadone dose at delivery (Finnegan LP, 1990), although studies have suggested that neonatal withdrawal reactions diminish with methadone doses of under 15mg daily.

If a woman is highly motivated to undergo **detoxification**, this may be supported, but should take place in an in-patient setting with obstetric supervision. The regime of choice in such cases has been a slow reduction in

methadone dosage at the rate of 2 to 2.5mg every 7 to 10 days; thus it will often prove impractical to arrange detoxification due to the long period of in-patient admission required to perform the intervention to the required standard of safety. However, a recent study of clonidine and/or methadone detoxification in 34 women in the second trimester found no evidence of foetal distress during detoxification, no foetal death and no delivery before 36 weeks. The authors (Dashe J et al, 1998) concluded that in selected patients, opioid detoxification can be accomplished safely during pregnancy.

Several studies have also appeared to demonstrate that buprenorphine (**Subutex**) is a safe alternative for maintenance prescribing in pregnancy, and may decrease the intensity of the neonatal opioid withdrawal syndrome (Johnson R. et al, 2001). However, due to the small numbers involved in these studies, and the need for replication of results, Subutex should not be commenced in pregnancy. Where a woman becomes pregnant whilst already prescribed Subutex, a judgement will have to be made regarding its continuation, taking into account the benefits and risks to the mother and foetus.

Opiate **intoxication** in pregnancy should only be treated with naloxone as a last resort due to the associated risk of spontaneous abortion or premature labour/stillbirth.

MANAGEMENT OF LABOUR

This is similar to any other woman, but pain relief needs special attention in the opiate-dependent patient. Additional opiates may not be very effective if receptors are already saturated, and early consideration should be given to administration of an epidural. Labour is more likely to be complicated by foetal distress than in the non-drug misusing woman.

TREATMENT OPTIONS FOR DRUG-EXPOSED NEONATES

NEONATAL OPIATE ABSTINENCE SYNDROME

Infants born to mothers who are chronically dependent on opiates during pregnancy (including methadone) are often born with a passive dependency which leads to an abstinence syndrome. Withdrawal symptoms from heroin and other short-acting opiates usually begin within 48 to 72 hours of birth, but may occur later, and are generally less predictable in their onset and course than with methadone. Neonatal abstinence syndrome occurs in about 60 to 80% of heroin or methadone-exposed infants (Finnegan & Ehrlich, 1990). Signs of neonatal opiate abstinence syndrome include the classical signs of adult opiate withdrawal characterised by autonomic hyperactivity and vomiting and diarrhoea, but also central nervous system signs such as irritability, tremulousness, hypertonia and excessive crying. Suckling may be exaggerated but poorly coordinated leading to poor nutrient intake and pulmonary aspiration. Abstinence-associated seizures may occur in a small proportion of infants.

Due to the unpredictable course of the syndrome, an objective scoring system should be employed to monitor the degree of withdrawal, such as that devised by Finnegan (Finnegan & Kaltenbach, 1992). In addition to supportive measures, various medications with CNS depressant action have been used to manage the withdrawal syndrome. The drug of first choice in the USA is paregoric (camphorated tincture of opium), but a variety of different drugs are used in the UK including chlorpromazine, methadone and morphine. The advantages of paregoric include its oral administration, lack of significant adverse effects and a wide margin of safety in dosage (Kandall, 1993). The management of the opiate-dependent infant should always occur in a specialist paediatric unit.

STIMULANTS

Cocaine-exposed infants show a very wide spectrum of effects, ranging from lack of obvious symptoms to neurobehavioural dysfunction, to more dramatic but less common complications such as seizures (Kramer, Locke et al, 1990) and cerebrovascular accidents (Chasnoff, Busey et al, 1986). If cocaine has been used recently before labour, there may be signs of neurotoxicity such as transient irritability and tremulousness. Following this period of central nervous system irritability there is often a period of hyporeactivity, lethargy and poor interaction with care-givers. There is no specific pharmacologic treatment indicated, although serious complications such as seizures may be treated with phenobarbital.

SEDATIVE-HYPNOTICS

Neonates who have been exposed to regular, large doses of barbiturates or benzodiazepines may demonstrate a withdrawal syndrome similar to the neonatal opiate withdrawal syndrome. Control can usually be achieved with phenobarbital treatment.

BREAST-FEEDING

Breast-feeding should be encouraged in general. Methadone does not enter the milk in significant quantities, and the methadone-maintained mother should usually breast-feed (McCarthy J, Posey B, 2000). Heavy benzodiazepine use, cocaine use, HIV and hepatitis C positive status are all **contraindications** to breast-feeding.

POSTNATAL PLANNING MEETING

Soon after delivery, a meeting should be held to decide on the appropriate support for the mother from, for example, the social worker and the general practitioner, and whether extra supervision is necessary. Continuing support, which may need to include parenting advice and skills training, is essential after discharge if the ideal outcome of keeping mother and child together is to be achieved. For further information see: 'Drug Using Parents: Policy guidelines for interagency working', Local Government Drugs Forum and Standing Conference on Drug Abuse (1997).

HIV AND VIRAL HEPATITIS IN PREGNANCY

PERINATAL TRANSMISSION OF HIV

A major breakthrough in the prevention of mother-to-child transmission of HIV type 1 (HIV-1) was made in 1994 with the demonstration that zidovudine (ZDV) administration to the mother resulted in a two-thirds decrease in transmission (Connor et al, 1994). Transmission rates with ZDV therapy are reduced from 20 to 25% to between 5 and 8% (Mayaux M et al, 1997). Transmission rates of HIV-2 (endemic in Africa, but rare in Europe) are in any case 10 times less than those of HIV-1. The mechanism of action of zidovudine in the prevention of vertical transmission is unclear. What is clear is that most transmission occurs in the final weeks or days of pregnancy (Mandelbrot L, 1997) which leads to the possibility that elective caesarean section may reduce transmission rates further (European Collaborative Study, 1996).

Early and aggressive therapy for HIV infection is becoming the standard of care, and therefore increasing numbers of women are receiving combination antiretroviral therapies for their own health (Minkoff H, Augenbraun M, 1997). Whether potent combination therapies will also have a protective effect against vertical transmission remains unknown, and the issue of fetal toxicity in the short and long-term is a cause for concern. At present, it appears reasonable to use combination regimes only when they are of established benefit to the mother, and not for the sole purpose of reducing transmission (Mandelbrot L, 1998).

HIV & BREASTFEEDING

The HIV-1 virus has been isolated from breastmilk and advice to HIV-infected mothers in the UK is to **avoid breastfeeding**. Whilst it is clear that HIV transmission may occur through breastfeeding, the prevalence of this is unknown. In contrast to Western countries, the WHO advice to HIV-infected mothers in countries where the commonest causes of infant mortality are infectious diseases and malnutrition, is to breastfeed. In such cases it is thought that the benefits of breastfeeding outweigh the risks.

- All pregnant women should be routinely tested for HbsAg and HIV-1 antibody; there are effective interventions to reduce the risk of infection of the infant.
- Pregnant women with a history of injecting drug use should probably be tested for HCV, in order to ensure appropriate follow-up of the offspring in the case of a positive result. There are however no effective interventions available to reduce the risk of mother-child transmission during pregnancy.
- Women infected with HIV and HCV are advised to avoid breastfeeding in Western countries.
- There is no contraindication to breastfeeding in women infected with HBV.

HEPATITIS A

Rarely, faecal-oral transmission may occur at the time of birth, and in-utero transmission has occurred (Michielsen P & Van Damme P, 1999). In those rare circumstances in which the mother has acute hepatitis A infection at the time of birth, immune serum globulin may be administered to the infant.

PERINATAL TRANSMISSION OF HEPATITIS B (HBV)

The rate of transmission from mother to offspring may be as high as 90% depending on the serological profile of the mother. Mothers who are positive for both HBsAg and HBeAg have an 80 to 90% chance of transmission with 85% of infected offspring becoming chronic carriers of HBsAg. Mothers who are positive for HBsAg and negative for HBeAg have only a 2 to 15% chance of transmission, and these babies rarely become carriers (Michielsen P & Van Damme P, 1999).

Similar to HIV and HCV infection, most maternal-child transmission seems to occur during or directly after delivery. As such, the neonates are suitable for postexposure prophylaxis. Newborns of HbsAg positive mothers should receive hepatitis B immunoglobulins within 12 hours after birth concurrently with first paediatric dose of hepatitis B vaccine. Vaccination should be completed at 1 and 6 months. This regime confers a protective efficacy of ≥ 90% (Michielsen P & Van Damme P, 1999).

HEPATITIS B AND BREASTFEEDING

Breastfeeding does not seem to play an important role in the transmission of Hepatitis B (Michielsen P & Van Damme P, 1999).

PERINATAL TRANSMISSION OF HEPATITIS C (HCV)

Reported rates of mother-to-child HCV transmission vary widely between 0 and 41% due to the small numbers and differences in the population studied. The largest study to date found 6 of 120 (5%) infants to be infected (Hunt C et al, 1997). Transmission rates in women also infected with HIV-1 are higher, possibly because HCV replication increases in cases of immune deficiency. The level of viraemia is the most important prognostic factor known (Ohto H et al, 1994), unlike HIV, where the viral load is not indicative of the likelihood of vertical transmission (Mandelbrot, 1998). In cases where plasma viral load determinations were available, most transmitting mothers had HCV RNA titers of 106/ml or more. As with HIV infection, most transmission is thought to occur around the time of delivery (Mandelbrot, 1998); this leaves open the possibility that elective caesarean section may reduce rates, although there is an absence of data to confirm or refute this hypothesis.

No intervention to decrease rates of peri-natal transmission yet exists. No vaccine is available. Post-exposure prophylaxis with immune globulin appears to offer little protection. Interferon therapy is still considered to be contraindicated in pregnancy, although its placental transfer has not been documented (Mandelbrot, 1998). Infection in the child may be diagnosed by the presence of HCV RNA in the child's serum after 1 month, or when anti-HCV antibodies are detected after 18 months (Bernard O, 1998). Most infected children develop chronic hepatitis, but the incidence of cirrhosis and hepatocellular carcinoma in later life are not yet known.

HCV AND BREASTFEEDING

HCV has been detected in some breastmilk samples, but only in some studies and at low concentrations. At present there is no biological or epidemiological proof of HCV transmission through breast-feeding. One must bear in mind, however, that the number of infants followed has been small (Mandelbrot, 1998). In the absence of good quality evidence, advice to HCV positive mothers in European countries is to avoid breastfeeding.

HEPATITIS D

This is rare in pregnant women and is uncommonly transmitted to infants. It is only active if there is co-infection with HBV (Michielsen P & Van Damme P, 1999)

HEPATITIS E

The hepatitis E virus is the only hepatitis virus that may affect the course of the pregnancy itself. Women who contract a hepatitis E infection during the third trimester of pregnancy have a relatively high probability of developing a fulminant hepatitis. It is likely to be the case that intrauterine infection occurs frequently and that this often leads to intrauterine death and abortion. It is particularly rare in the UK and occurs most frequently in epidemics in Asia, South and Central America (Michielsen P & Van Damme P, 1999).

HEPATITIS G

Preliminary data indicate that the risk of vertical transmission seems to be high in the region of 30 to 60%, associated with high maternal viraemia. The clinical significance of HGV remains to be established (Michielsen P & Van Damme P, 1999).